

THE ELECTROCARDIOGRAM IN MYXŒDEMA

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The characteristics of the electrocardiogram in myxœdema and their regression under adequate replacement therapy have been frequently discussed since they were defined (Zondek, 1918). However, a search of previous reports has revealed only sporadic studies concerned with the *early* effects of thyroid medication upon the electrocardiogram, either alone or in relation to the other parameters of thyroid function. The recent investigations in seven patients throw light upon several as yet ill-defined aspects of thyroid activity upon the heart muscle, and for this reason they are now reported.

CASE REPORTS

Case 1. A 46-year-old woman had been suffering from anginal pain for the past four years, without obtaining substantial benefit from the commonly employed coronary dilators. Examination revealed not only arteriosclerotic and hypertensive cardiovascular disease, but also frank myxœdema with a B.M.R. of -23 per cent. The cardiogram showed low voltage with flat or absent P and T waves. After 240 µg. tri-iodothyronine (T3) in two days a left strain pattern became manifest which henceforth remained stationary. Despite rapid reduction of the daily dosage the patient progressively became euthyroid and remained so with 0.4 g. desiccated thyroid a week.

Case 2. A 55-year-old woman had been under treatment for myxœdema for the past 10 years. She required a daily dose of 0.15 g. desiccated thyroid in order to remain symptom-free. Frequent attempts to reduce dosage in view of her associated arteriosclerotic and hypertensive cardiovascular disease were unsuccessful both objectively and subjectively. In October 1961 the patient had a severe præcordial pain suggestive of an acute myocardial infarction. Despite the lack of corroborative laboratory and electrocardiographic evidence her attending physician discontinued thyroid therapy. Ten weeks later the patient presented with a recurrence of her myxœdema (serum cholesterol 390 mg. per cent, B.M.R. of -19 per cent, I¹³¹ uptake 4 per cent at 24 hours, and 3 per cent at 48 hours). The cardiogram, which eight weeks after the withdrawal of thyroid medication had shown inverted T waves in leads I, II, AVF, and V3-6, now showed a distinctly low voltage with practically isoelectric T waves in most limb and chest leads (Fig. 1A). Twenty-four hours after the first dose of 40 µg. T3 the T waves in V3-6 had again become negative (Fig. 1B), there being yet no other appreciable effect of thyroid therapy. After six days of therapy the T waves had become less deeply inverted and there was a slight increase in voltage. At the same time the patient first noted some subjective improvement together with a weight loss of 3 kg. and a decrease of her puffiness. Henceforth there was a gradual uniform improvement until 26 days after the onset of therapy the patient was clinically euthyroid with a B.M.R. of -9 per cent while the cardiogram had reverted to normal (Fig. 1C), although the voltage remained at the lower range of normal. The size and configuration of the heart shadow had not changed during the whole period of observation.

Case 3. A 21-year-old woman had been myxœdematous since early childhood. Owing to irregular and inadequate thyroid therapy both her somatic and mental development had remained at an infantile level. After she had again discontinued thyroid therapy for three months, she was obviously myxœdematous with a

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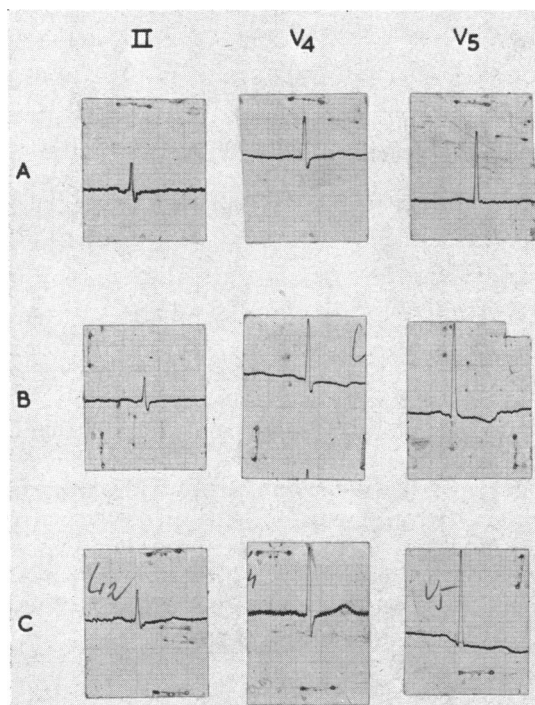


FIG. 1.—Case 2. A 55-year-old woman with myxœdema and arteriosclerotic cardiovascular disease. (A) Leads II, V4, and V5 before therapy. (B) The same leads 24 hours after first dose of 40 μ g. T3. (C) The same leads after 26 days of therapy.

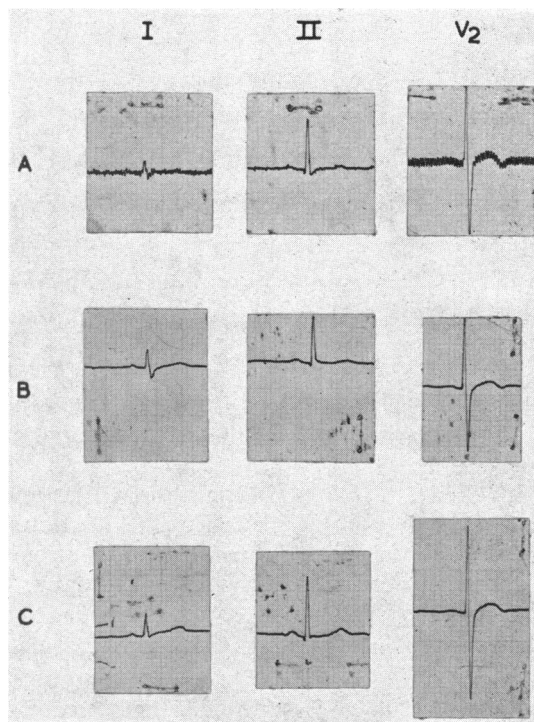


FIG. 2.—Case 3. A 21-year-old woman with myxœdema. (A) Leads I, II, and V2 before therapy. (B) The same leads 24 hours after first dose of 40 μ g. T3. (C) The same leads after almost two months of therapy.

B.M.R. of -17 per cent, a serum cholesterol of 330 mg./100 ml. and a I^{131} uptake of 4.5 per cent at two hours and 3.3 per cent at 24 hours. The cardiogram showed practically absent respectively low P and T waves in most limb and chest leads, and biphasic T waves in leads V2-3 (Fig. 2A).

A distinct increase in wave height with restoration of the T wave in V2-3 was already evident 24 hours after administration of 40 μ g. T3 (Fig. 2B), the clinical symptoms being unchanged. With continued therapy there was no further change in the tracing despite a progressive amelioration of the clinical findings and, after 18 days, even signs of mild toxicity (increased nervous excitability, sweating and tachycardia) which necessitated a reduction of dosage to 30 μ g. a day. One week later the patient was transferred to equivalent amounts of desiccated thyroid (we have found that 0.1 g. of the local preparation correspond to 30 μ g. T3) with clinically satisfactory results. However, after only one more month of this therapy a further rise in voltage was noted in the record (Fig. 2C).

Case 4. A 57-year-old married woman had been hypothyroid for about 30 years during which time her symptoms and signs were controlled with small amounts of desiccated thyroid (0.4-0.5 g. per week). For about a year her condition had gradually deteriorated. (It was later established that the patient had taken ineffective thyroid tablets.) Upon re-examination she was found to be myxœdematous. The serum cholesterol level was 672 mg./100 ml., and the B.M.R. was -20 per cent. I^{131} uptake was 5.5 per cent at two hours, and 5 per cent at 24 hours. The heart was of normal size and shape on x-ray picture except for a slight bulging of the left atrium. Yet the cardiogram showed a very low voltage with practically invisible P and T waves in the limb leads.

After 10 μ g. T3 there was no change whatsoever in the patient's condition. Nine hours after 15 μ g. (administered after a suitable interval) there was a slight rise of the P and T waves; no further change occurred after two more doses of 15 μ g. each. When during the following 10 days larger doses were employed (25 μ g.

daily for six days, 40 and 60 μ g. daily each for two days), the voltage became somewhat higher and there was improvement in the patient's general condition. However, neither the cardiogram nor the other criteria of thyroid function reverted to normal. Thereafter, T3 was substituted by desiccated thyroid. After five days of 0.2 g. daily the tracing became normal, and the patient became euthyroid. Later she developed subjective complaints (nervous irritability, sleeplessness) and the daily dose was gradually decreased to the former maintenance dose (0.5 g. weekly) without untoward effects upon either the cardiogram or the general state.

There was no change in the size or configuration of the heart shadow during the whole period of observation.

Case 5. A 58-year-old woman was under my treatment for about 25 years for frank myxœdema. Her thyroid requirements usually averaged 0.2 g. daily, but repeatedly rose to 0.4 g. daily for protracted periods. Early in 1963 she presented with a gross recurrence of her myxœdema because of temporary discontinuation of replacement therapy (I^{131} uptake 6 per cent at two hours and 1.9 per cent at 24 hours). The cardiogram displayed practically isoelectric P and T waves in the limb leads (Fig. 3A).

Twenty-four hours after the administration of 40 μ g. T3 there already was a distinct increase in wave height (Fig. 3B) which however did not become more prominent after the second dose of 40 μ g. Even when the daily dosage was increased to 60 μ g. for two days and to 80 μ g. for three days, the tracing did not show any improvement; if anything, there was a slight decrease in voltage. Only after three days' treatment with 100 μ g. daily, did the cardiogram revert to normal (Fig. 3C). The remainder of the clinical features were unaltered, although the patient admitted that she felt better. Nevertheless, in view of her age an attempt was made to reduce dosage, and for the following three weeks 60 μ g. daily were administered. Thereupon a decrease in voltage was noted in the electrocardiogram, and the patient claimed she felt "more heavy." Dosage was therefore once more raised to 100 μ g. daily which was then replaced by equivalent amounts of desiccated thyroid (0.35 g. daily). Under this régime the electrocardiogram again reverted to normal and the patient also became progressively euthyroid. While complaining of præcordial pain and other unpleasant sensations in the heart region during tri-iodothyronine administration, equivalent amounts of whole thyroid were perfectly tolerated.

Case 6. A 37-year-old woman had obvious myxœdema for a number of years. Adequate compensation had never been achieved because of the patient's lack of co-operation due to an associated paranoid psychosis. After taking no medicine for about three months she presented again with symptoms of myxœdema (protein-bound iodine¹²⁷: 1.7 μ g./100 ml.) while the cardiogram displayed a typical low voltage pattern.

The administration of 30 μ g. T3 daily during one week produced no change either in the cardiogram or the symptoms and signs. After 10 days of 50 μ g. daily there was a distinct improvement in the clinical findings with a weight loss of 3.5 kg., yet the cardiogram remained unchanged. Only after another month of continued therapy, when clinically the patient was more or less euthyroid, did the cardiogram display a slight increase in voltage.

Case 7. A 50-year-old woman had undergone total thyroidectomy for a papillary adenocarcinoma of the thyroid five years ago. Various attempts at adequate replacement therapy had been refused by the patient who claimed that she could not tolerate more than $\frac{1}{2}$ grain desiccated thyroid weekly. This quantity had been regularly taken for the past year or so when she was admitted. She complained of some mental and physical lethargy, increased sensitivity to cold, and obstinate constipation.

Upon examination the patient displayed a slow pulse rate (64/min.), some dryness of the skin, and very sluggish tendon reflexes. Serum cholesterol was 380 mg./100 ml., and the B.M.R. was -28 per cent. I^{131}

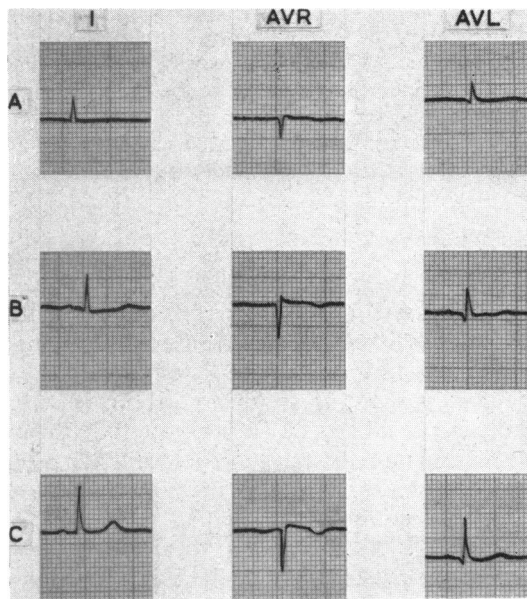


FIG. 3.—Case 5. A 58-year-old woman with myxœdema. (A) Leads I, AVR, and AVL before therapy. (B) The same leads after 40 μ g. T3. (C) The same leads after three days of 100 μ g. T3 each.

uptake was 5 per cent at two hours, and 10.5 per cent at 24 hours. The cardiogram showed a very low voltage with the P and T waves being practically absent in the limb leads, and very low in the chest leads.

Administration of progressively increasing amounts of T₃ (up to 60 µg. a day) during four weeks resulted in the gradual disappearance of the clinical symptoms with a weight loss of 4.5 kg., a rise of the pulse rate to 80, a drop of serum cholesterol to 220 mg./100 ml., and a rise of the B.M.R. to -9 per cent. This remission was maintained with 0.15 g. desiccated thyroid a day, 0.1 g. having been inadequate in this respect. However, the cardiogram showed a distinct rise in voltage after four months of therapy.

DISCUSSION

It is a well-documented, but often insufficiently appreciated, fact that the responsiveness of the peripheral tissues to lack of thyroid hormone is highly variable. The muscle fibres of the heart are no exception to the rule. Consequently the behaviour of the electrocardiogram need not conform to the kind and degree of myxœdematous changes in the other tissues. The tracing may—though only rarely—display a normal pattern in the presence of a fully-developed myxœdema, or conversely, it may be more extensively involved than might be suggested by the other clinical features.

The observations here presented upon seven patients with a typical electrocardiogram of myxœdema confirm the individual and variable responsiveness of the heart muscle to substitution therapy.

In one patient (Case 1) the administration of large doses resulted 48 hours later in the appearance of a previously masked left strain pattern due to her arteriosclerotic cardiovascular disease, as previously reported by Means (1948) and Zondek (1959). A similar sequence was observed in Case 2 also suffering from myxœdema combined with arteriosclerotic heart disease. In this patient also the first effect of substitution therapy, observed 24 hours after a much smaller dose, was the production of negative T waves in the left ventricular leads. However, in contradistinction to Case 1 in whom no further changes were noted, the inverted T waves in Case 2 gradually became positive during the course of continued therapy. It therefore follows that in Case 2 negativity of the T waves was myxœdematous, while in Case 1 it was arteriosclerotic in nature. This difference in interpretation would not have been revealed without follow-up studies.

In four patients (Cases 2-5) the cardiogram already displayed notable changes 24 hours (or even earlier) after the administration of the first dose of T₃, this being in fact the first sign of effective replacement therapy. In two of them (Cases 2 and 4) the tracing subsequently became more or less normal in conformity with the general clinical trend. In two others (Cases 3 and 5) continuation of therapy (in Case 5 even with much higher doses than originally employed) failed for more or less protracted periods of time to produce a further increase in voltage, although the other myxœdematous symptoms and signs gradually disappeared; in Case 3 even clinically manifest signs of overdosage occurred. It appears that in these two patients the heart muscle, after an initial prompt response, remained in a state of comparative refractoriness which was overcome with time only. In two patients the cardiogram showed the first signs of response only after six weeks (Case 6) and 16 weeks of therapy (Case 7). During this time the other clinical features had already reacted satisfactorily, indicating an even greater refractoriness of the heart muscle to thyroid hormone. It is worthy of note that these last two patients had never before received adequate substitution therapy. This was also true of Case 3 who, notwithstanding her early prompt response, had behaved in a similar manner. It appears therefore as though a protracted deficiency of thyroid hormone will induce variable degrees of hypo-reactivity of the heart muscle. Complete unresponsiveness presumably is due to irreversible organic changes (fibrous tissue replacement) known to occur in long-standing myxœdema. Minor degrees, as in Cases 3, 5, 6, and 7, may well be purely functional in nature; this possibility should be the subject of further studies. The widely variable reactivity of the heart muscle to thyroid hormone displayed by these seven patients exactly agrees with the postulate expressed by the "peripheral theory" (Zondek, 1924) that the activity of hormonal substances depends to a large extent upon the condition and responsiveness of the peripheral target organs.

The time of appearance of electrocardiographic changes subsequent to the institution of replacement therapy is also important from another angle. It is frequently held that the cardio-circulatory effects of thyroid hormone are not primary in nature, but secondary to its metabolic activities, chiefly its stimulation of oxygen consumption (Neter, 1934; Rihl, Oestreicher, and Reiss, 1936; Fishburne and Cunningham, 1938). The occurrence of electrocardiographic alterations 24 hours or even less after the onset of therapy, before other effects of therapy became discernible, favours the opposite view, namely that of a direct effect of thyroid hormone upon the heart (Meyer and Wertz, 1939; Meyer and Marine, 1942; Leblond and Hoff, 1944; Hoffmann, Hoffmann, and Talesnik, 1948).

Another point of long-standing contention, which deserves comment in the light of the foregoing observations, concerns the patho-physiological foundations of the electrocardiogram in myxœdema. Two factors appear to be responsible as already postulated in the original descriptions of the myxœdema heart (Zondek, 1918, 1919, 1920): (1) increased watery imbibition, and (2) "hypotonicity" of the heart muscle due to abnormal vagus tonus. A major role of the neurogenic factor may be ruled out in the present series, as in the majority of cases electrocardiographic changes were noted before any neuro-circulatory effects of thyroid hormone such as an acceleration of the heart rate. It may therefore be assumed that the hydration factor was of primary importance. The present consensus of opinion seems to favour a major role of pericardial effusion in the production of the cardio-graphic patterns (Kern *et al.*, 1949; Marks and Roof, 1953; Hamolsky, Kurland, and Freedberg, 1961). Conversely, it has been my opinion that only minor shifts in the intercellular and intracellular water exchange of the cardiac muscle were required for this purpose, a view that the present observations seem to support. It is hardly possible that the small amounts of thyroid producing electrocardiographic alterations in short periods of time would have had appreciable effects upon such substantial fluid accumulations as those present in the pericardial sac. The failure of the heart shadow to decrease in size along with the appearance of a normal cardiogram in some of the patients is another argument against a major role of pericardial effusion in the pathogenesis of the cardio-graphic abnormalities.

It is generally acknowledged that the biological properties of T3 do not qualitatively differ from those of other thyroid compounds. This conclusion also seems to apply to its action upon the heart muscle. From a practical point of view T3 may have one possible advantage over more slowly acting substances, and this concerns its suitability for the initiation of therapy. The impression was gained that the dosage with which the first electrocardiographic response was obtained might in certain cases serve as a useful therapeutic guide, inasmuch as it was usually found to correspond more or less to the dose requirements for maintenance therapy. However, for continued replacement therapy desiccated thyroid is still the treatment of choice. Owing to its more protracted and uniform action whole thyroid seems not only to be better tolerated, especially by the elderly patient with associated organic disease of the heart; it may also occasionally permit some reduction of dosage.

SUMMARY

The changing pattern of the electrocardiogram was studied in seven patients with myxœdema before and during the early stages of thyroid substitution therapy. In one patient a previously masked left strain pattern became manifest 48 hours after the start of therapy with a rapidly acting thyroid compound (tri-iodothyronine). In four patients the cardiogram displayed distinct changes 24 hours (or earlier) after the first dose of 40 μ g. (or less) of tri-iodothyronine, this being in fact the first sign of effective replacement therapy. In two of them the tracing progressively reverted to normal while the clinical signs also regressed. In the other two patients the early electrocardiographic response was followed by a period of unresponsiveness during which the other symptoms and signs of myxœdema disappeared. In these last two patients the electrocardiogram displayed a delayed response indicating that in them the heart muscle was comparatively more refractory to thyroid hormone than were the other peripheral tissues.

The implications of these observations are discussed. It is emphasized that the short-term effects of small amounts of thyroid upon the myxœdema electrocardiogram argue in favour of (i) a primary action of thyroid hormone upon the cardio-circulatory system independent of the metabolic activities of the hormone, (ii) minute changes in the intracardiac water balance as the patho-physiological foundation of the occurrence and regression of the electrocardiographic anomalies in myxœdema, and (iii) the suitability of rapidly-acting thyroid compounds for the introduction of therapy, in contradistinction to their inferiority to desiccated thyroid for purposes of long-term treatment. The role of the peripheral target organs in determining the mode and extent of hormonal activity is discussed afresh in the light of these observations.

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